EXHIBIT A

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Deborah A. Jaskot, M.S., RAC
Executive Director, Regulatory Affairs

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CONFIDENTIAL
July 2, 2004

VIA FEDERAL EXPRESS DELIVERY:
Procter & Gamble Pharmaceuticals
11450 Grooms Road
Cincinnati, Ohio 45242-1434

The Procter & Gamble Company
Miami Valley Labs
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Cincinnati, Ohio 45247

The Procter & Gamble Company
8500 Governors Hill
Mason, Ohio 45040

VIA FEDERAL EXPRESS DELIVERY:
The Procter & Gamble Company
6090 Center Hill Avenue
Cincinnati, Ohio 45224

Merck & Company, Inc.
RY60-30
P.O. Box 2000
Rahway, New Jersey 07065

Re: Patent Certification Notice – U.S. Patent Nos. 5583122, 6096342, 6165513, 5994329 and 6015801
Risedronate Sodium Tablets, 5 mg, 30 mg and 35 mg
Teva Pharmaceuticals USA, Inc.'s ANDA 77-132

Dear President or Counsel:

The purpose of this communication is to provide the notice and information required by 21 U.S.C. § 355(j)(2)(B)(i) and (ii) (sections 505(j)(2)(B)(i) and (ii) of the Food, Drug and Cosmetic Act) that Teva Pharmaceuticals USA, Inc. ("Teva"), a Delaware corporation with its principal place of business at 1090 Horsham Road, North Wales, Pennsylvania, has submitted an ANDA for Risedronate Sodium Tablets, 5 mg, 30 mg and 35 mg, which contains the required bioavailability and/or bioequivalence data and Paragraph IV certification with respect to U.S. Patent Nos. 5583122, 6096342, 6165513, 5994329 and 6015801.

A detailed statement of the factual and legal bases for Teva's position regarding these patents is provided herein. Teva reserves the right to assert additional grounds, reasons and authorities for its position that the aforesaid patents are invalid, unenforceable, or will not be infringed.

In addition, please find enclosed an Offer of Confidential Access pursuant to 21 U.S.C. §355(j)(2)(C)(i)(III).

Sincerely,

Deborah Jaskot

Deborah A. Jaskot
Executive Director, Regulatory Affairs

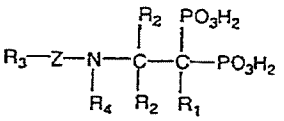
Confidential: Teva Pharmaceuticals USA, Inc.'s Detailed Statement Of The Factual And Legal Bases For Its Opinion That U.S. Patents Nos. 5,583,122, 5,994,329, 6,015,801, 6,096,342, And 6,165,513 Are Invalid, Unenforceable Or Not Infringed By The Manufacture, Use Or Sale Of Teva's 5, 30 And 35 Mg Risedronate Sodium Tablets

This is the detailed statement of Teva Pharmaceuticals USA, Inc. ("Teva"), pursuant to Section 505(j)(2)(B)(ii) of the Food and Drug Act (codified at 21 U.S.C. § 355(j)(2)(B)(ii)), and 21 C.F.R. § 314.95(c), of its factual and legal bases for its opinion that U.S. Patents Nos. 5,583,122 ("the '122 patent"), 5,994,329 ("the '329 patent"), 6,015,801 ("the '801 patent"), 6,096,342 ("the '342 patent"), and 6,165,513 ("the '513 patent") are invalid, unenforceable, or not infringed, either literally or under the doctrine of equivalents, by the manufacture, use or sale of Teva's 5, 30 and 35 mg risedronate sodium tablets ("Teva's tablets"), for which this detailed statement is submitted. The bases for Teva's opinion follow.

I The '122 Patent

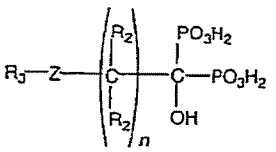
The '122 patent, entitled *Pharmaceutical Compositions Containing Geminal Diphosphonates*, issued December 10, 1996, from application S/N 806,155 (filed December 6, 1985), and is a continuation-in-part ("CIP") of abandoned application S/N 684,543 (filed December 21, 1984). Assigned on its face to The Procter & Gamble Company, Cincinnati, Ohio, the '122 patent lists as inventors James J. Benedict and Christopher M. Perkins, and contains twenty-three (23) claims, seven (7) of which are independent. The '122 patent is due to expire December 10, 2013.

1. A diphosphonic acid compound, or a pharmaceutically-acceptable salt or ester thereof, having the structure:



wherein Z is a pyridine ring; R_1 is hydrogen substituted or unsubstituted amino, amido, hydroxy, C_1 -C_6 alkoxy, halogen, carboxylate, a substituted or unsubstituted, a saturated or unsaturated hydrocarbon chain having from 1 to 6 carbon atoms, substituted or unsubstituted phenyl, or substituted or unsubstituted benzyl; R_2 is hydrogen, or a substituted or unsubstituted, saturated or unsaturated hydrocarbon chain having from 1 to 4 carbon atoms; R_3 is hydrogen, a substituted or unsubstituted, saturated or unsaturated hydrocarbon chain having from 1 to 6 carbon atoms, substituted or unsubstituted benzyl, hydroxy, halogen, C_1-C_6 alkoxy, amino, substituted amino, substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, carbonyl, nitro, amido, or carboxylate; and R_4 is hydrogen, a substituted or unsubstituted, saturated or unsaturated hydrocarbon chain having from 1 to 4 carbon atoms, or acetyl; and wherein said substituted R_1, R_2, R_3 and R_4 groups are independently substituted with methyl, ethyl, amino, chloro, nitro, methoxy, hydroxy, acetamido, or acetate.

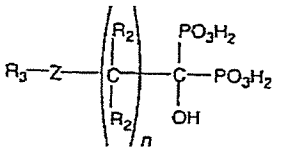
2. A diphosphonic acid compound, or a pharmaceutically-acceptable salt or ester thereof, having the structure:



wherein Z is a pyridine ring; n is 0 or 1; R_2 is hydrogen, or a substituted or unsubstituted, saturated or unsaturated hydrocarbon chain having from 1 to 4 carbon

atoms; and R_3 is hydrogen, a substituted or unsubstituted, saturated or unsaturated hydrocarbon chain having from 1 to 6 carbon atoms, substituted or unsubstituted benzyl, hydroxy, halogen, C_1-C_6 alkoxy, amino, substituted amino, substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, carbonyl, nitro, amido, or carboxylate; and wherein said substituted R_2 and R_3 groups are independently substituted with methyl, ethyl, amino, chloro, nitro, methoxy, hydroxy, acetamido, or acetate.

3. A diphosphonic acid compound, or a pharmaceutically-acceptable salt or ester thereof, having the structure:

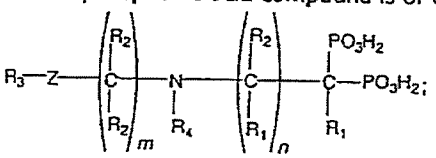


wherein Z is a pyridine ring n is 1; R_2 is hydrogen, or a substituted or unsubstituted, saturated or unsaturated hydrocarbon chain having from 1 to 4 carbon atoms; and R_3 is hydrogen, a substituted or unsubstituted, saturated or unsaturated hydrocarbon chain having from 1 to 6 carbon atoms, substituted or unsubstituted benzyl, hydroxy, halogen, C_1-C_6 alkoxy, amino, substituted amino, substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, carbonyl, nitro, amido, or carboxylate; and wherein said substituted R_2 and R_3 groups are independently substituted with methyl, ethyl, amino, chloro, nitro, methoxy, hydroxy, acetamido, or acetate.

4. A diphosphonic and acid compound, or pharmaceutically-acceptable salt or ester thereof, which is 2-(3-pyridyl)-1-hydroxyethane diphosphonic acid.

5. A pharmaceutical composition comprising:

(a) a geminal diphosphonic acid compound, or a pharmaceutically-acceptable salt or ester thereof, at a level providing from 0.001 to 600 mg of phosphorus in said composition, wherein said diphosphonic acid compound is of the formula:



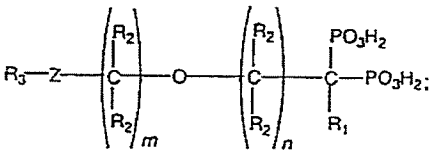
wherein Z is a pyridine ring; m+n is an integer from 0 to 5; R_1 is hydrogen, substituted or unsubstituted amino, amido, hydroxy, C_1-C_6 alkoxy, halogen, carboxylate, a substituted or unsubstituted, saturated or unsaturated hydrocarbon chain having from 1 to 6 carbon atoms, substituted or unsubstituted phenyl, or substituted or unsubstituted benzyl, except that when n=0, then R_1 is hydrogen, a substituted or unsubstituted, saturated or unsaturated hydrocarbon chain having from 1 to 6 carbon atoms, substituted or unsubstituted phenyl, or substituted or unsubstituted benzyl; R_2 is hydrogen, or a substituted or unsubstituted, saturated or unsaturated hydrocarbon chain having from 1 to 4 carbon atoms; R_3 is hydrogen, a substituted or unsubstituted, saturated or unsaturated hydrocarbon chain having from 1 to 6 carbon atoms, substituted or unsubstituted benzyl, hydroxy, halogen, C_1-C_6 alkoxy, amino, substituted amino, substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, carbonyl, nitro, amido, or carboxylate; and R_4 is hydrogen, a substituted or

unsubstituted, saturated or unsaturated hydrocarbon chain having from 1 to 4 carbon atoms, or acetyl;

(b) a pharmaceutically-acceptable carrier.

6. A pharmaceutical composition comprising:

(a) a geminal diphosphonic acid compound, or a pharmaceutically-acceptable salt or ester thereof, at a level providing from 0.001 to 600 mg of phosphorus in said composition, wherein said diphosphonic acid compound is of the formula:



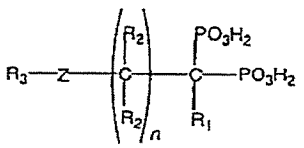
wherein Z is a pyridine ring; m+n is an integer from 0 to 5; R_1 is hydrogen, substituted or unsubstituted amino, amido, hydroxy, C_1-C_6 alkoxy, halogen, carboxylate, a substituted or unsubstituted, saturated or unsaturated hydrocarbon chain having from 1 to 6 carbon atoms, substituted or unsubstituted phenyl, or substituted or unsubstituted benzyl, except that when n=0, then R_1 is hydrogen, a substituted or unsubstituted, saturated or unsaturated hydrocarbon chain having from 1 to 6 carbon atoms, substituted or unsubstituted phenyl, or substituted or unsubstituted benzyl; R_2 is hydrogen, or a substituted or unsubstituted, saturated or unsaturated hydrocarbon chain having from 1 to 4 carbon atoms: and R_3 is hydrogen, a substituted or unsubstituted, saturated or unsaturated hydrocarbon chain having from 1 to 6 carbon atoms, substituted or unsubstituted benzyl, hydroxy, halogen, C_1-C_6 alkoxy, amino, substituted amino, substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, carbonyl, nitro, amido, or carboxylate; and

(b) a pharmaceutically-acceptable carrier.

* * * *

11. A pharmaceutical composition comprising:

(a) a geminal diphosphonic acid compound or a pharmaceutically-acceptable salt or ester thereof, at a level providing from 0.001 to 600 milligrams phosphorus in said composition, wherein said compound is of the formula:



wherein Z is a pyridine ring; n is 0 or 1; R_1 is hydrogen, substituted or unsubstituted amino, amido, hydroxy, C_1-C_6 alkoxy, halogen, carboxylate, a substituted or unsubstituted, saturated or unsaturated hydrocarbon chain having from 1 to 6 carbon atoms, substituted or unsubstituted phenyl, or substituted or unsubstituted benzyl; R_2 is hydrogen, or a substituted or unsubstituted, saturated or unsaturated hydrocarbon chain having from 1 to 4 carbon atoms; and R_3 is hydrogen, a substituted or unsubstituted, saturated or unsaturated hydrocarbon chain having from 1 to 6 carbon atoms, substituted or unsubstituted benzyl, hydroxy, halogen, C_1-C_6 alkoxy, amino, substituted amino, substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl,

carbonyl, nitro, amido, or carboxylate; and wherein said substituted R_1, R_2 and R_3 groups are independently substituted with methyl, ethyl, amino, chloro, nitro, methoxy, hydroxy, acetamido, or acetate; and

(b) a pharmaceutically-acceptable carrier.

Dependent claims 7 and 17 depend from claim 5, whereas claims 9 and 19 depend from claim 7. Claims 8 and 18 depend from claim 6, whereas claim 10 depends from claim 8. Claims 12-13 depend from claim 11, whereas claims 14 and 20 depend from claim 12. Claims 15, 16 and 21 depend from claim 14, while claim 22 depends from claim 15 and claim 23 depends from claim 16.

The dependent claims further define: the value of $m + n$ (claims 7-8); the substituents (claims 9-10 and 13); the n value as equal to one (claim 12); the diphosphonic acid selected from a Markush group (claim 14); the specific diphosphonic acid (claim 15); and, methods of treating diseases associated with abnormal calcium and phosphate metabolism (claims 17-23).

II The '329 Patent

The '329 patent, entitled *Method For Inhibiting Bone Resorption*, issued November 30, 1999, from application S/N 09/134,214 (filed August 14, 1998), which is a continuation of application No. PCT/US98/14796 (filed July 17, 1998), and is related to provisional application S/Ns 60/053,535 (filed July 23, 1997) and 60/053,351 (filed July 22, 1997). Assigned on its face to Merck & Co., Inc., Rahway, N.J., the '329 patent lists as inventors Anastasia G. Daifotis, Arthur C. Santora, II and A. John Yates, and contains forty-four (44) claims, of which four (4) are independent. The '329 patent is due to expire July 17, 2018.

1. A method for inhibiting bone resorption in a mammal in need thereof comprising orally administering to said mammal a pharmaceutically effective amount of a bisphosphonate as a unit dosage according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

* * * *

16. A method for treating osteoporosis in a mammal in need thereof comprising orally administering to said mammal a pharmaceutically effective amount of a bisphosphonate as a unit dosage according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

* * * *

30. A method for preventing osteoporosis in a mammal in need thereof comprising orally administering to said mammal a pharmaceutically effective amount of a bisphosphonate as a unit dosage according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

* * * *

44. A kit comprising at least one pharmaceutically effective unit dosage of a bisphosphonate for oral administration according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

Dependent claim 2 depends from claim 1, whereas claims 3 and 5 depend from claim 2. Claim 4 depends from claim 3, and claim 6 depends from claim 4. Claims 7, 10, 12 and 14 depend from claim 6, while claim 8 depends from claim 7 and claim 9 depends from claim 8. Claims 11, 13 and 15 depend from the immediately preceding claims, *i.e.*, claims 10, 12 and 15.

Claim 17 depends from claim 16 and claims 18 and 20 depend from claim 17. Claim 19 depends from claim 18, whereas claim 21 depends from claim 19. Claims 22, 24, 26 and 28 depend from claim 21, while claims 23, 25, 27 and 29 depend from the immediately preceding claims, *i.e.*, claims 22, 25, 26 and 28, respectively. Claim 31 depends from claim 30, while claims 32 and 34 depend from claim 31. Claim 33 depends from claim 32 and claim 35 depends from claim 33. Claims 36, 38, 40 and 42 depend from claim 35, whereas claims 37, 39, 41 and 43 depend from the immediately preceding claims, *i.e.*, claims 36, 39, 40 and 42, respectively.

The dependent claims further define: the biphosphonate (claims 2-3, 5-17-18, 20, 31-32 and 34); the pharmaceutically acceptable salt (claims 4, 19 and 33); the mammal treated (claims 6, 21, 35); the dosing interval (claims 7, 10, 12, 14, 22, 24, 26, 28, 36, 38, 40 and 42); and, the dosage amount (claims 8-9, 11, 13, 15, 23, 25, 27, 29, 37, 39, 41 and 43).

III The '801 Patent

The '801 patent, entitled *Method For Inhibiting Bone Resorption*, issued January 18, 2000, from application S/N 09/134,215 (filed August 14, 1998), which is a continuation-in-part of application No. PCT/US98/14796 (filed July 17, 1998), and is related to provisional application S/Ns 60/053,535 (filed July 23, 1997) and 60/053,351 (filed July 22, 1997). Assigned on its face to Merck & Co., Inc., Rahway, N.J., the '801 patent lists as inventors Anastasia G. Daifotis, A. John Yates and Arthur C. Santora, II, and contains fifty-nine (59) claims, of which four (4) are independent. The '801 patent is due to expire July 17, 2018.

> 1. A method for treating a condition or disease state in a mammal, said disease state or condition selected from the group consisting of Paget's disease, abnormally increased bone turnover, periodontal disease, tooth loss, bone fractures, metastatic bone disease, hypercalcemia of malignancy, and multiple myeloma, said method comprising orally administering to said mammal a pharmaceutically effective amount of a unit dosage of a bisphosphonate according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.
>
> * * * *
>
> 15. A method for preventing a condition or disease state in a mammal in need thereof, said disease state or condition selected from the group consisting of Paget's disease, abnormally increased bone turnover, periodontal disease, tooth loss, bone fractures, metastatic bone disease, hypercalcemia of malignancy, and multiple myeloma, said method comprising orally administering to said mammal a pharmaceutically effective amount of a unit dosage of a bisphosphonate according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.
>
> * * * *
>
> 29. A method for treating a condition or disease state in a mammal, said disease state or condition selected from the group consisting of Paget's disease, abnormally increased bone turnover, periodontal disease, tooth loss, bone fractures, metastatic bone disease, hypercalcemia of malignancy, and multiple myeloma, said method comprising sequentially orally administering to said mammal a pharmaceutically effective amount of a unit dosage of a histamine H2 receptor blocker or a proton pump inhibitor and a unit dosage of a bisphosphonate according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.
>
> * * * *

> 44. A method for preventing a condition or disease state in a mammal in need thereof, said disease state or condition selected from the group consisting of Paget's disease, abnormally increased bone turnover, periodontal disease, tooth loss, bone fractures, metastatic bone disease, hypercalcemia of malignancy, and multiple myeloma, said method comprising sequentially orally administering to said mammal a pharmaceutically effective amount of a unit dosage of a histamine H2 receptor blocker or a proton pump inhibitor and a unit dosage of a bisphosphonate according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

Dependent claim 2 depends from claim 1, whereas claims 3 and 5 depend from claim 2. Claim 4 depends from claim 3, whereas claim 6 depends from claim 4. Claims 7, 9, 11 and 13 depend from claim 6, while claim 8 depends from claim 7 and claim 10 depends from claim 8. Claim 12 depends from claim 11 and claim 14 depends from claim 13.

Dependent claim 16 depends from claim 15, whereas claims 17 and 19 depend from claim 16. Claim 18 depends from claim 17 and claim 20 depends from claim 18. Claims 21, 23, 25 and 27 depend from claim 20, whereas claims 22 and 30 depend from claim 21. Claims 24, 26 and 28 depend from the immediately preceding claim, *i.e.*, claims 23, 25 and 27, respectively. Claim 31 depends from claim 30. Claims 32 and 34 depend from claim 31 and claim 33 depends from claim 32. Claim 35 depends from claim 33 and claims 36, 38, 40 and 42 depend from claim 35. Claims 37, 39 and 43 depend from the immediately preceding claim, *i.e.*, claims 36, 38 and 42, respectively.

Claim 41 depends from claim 39. Claim 45 depends from claim 44 and claim 46 depends from claim 45. Claims 47 and 49 depend from claim 46, while claim 48 depends from claim 47. Claim 50 depends from claim 48, whereas claims 51, 53, 55 and 57 depend from claim 50. Claim 52 depends from claim 51. Claims 54, 56 and 58 depend from the immediately preceding claims, *i.e.*, claims 53, 55 and 57, respectively.

The dependent claims further define: the bisphosphonate (claims 2-3, 5, 16-17, 19, 31, 34, 46 and 49); the pharmaceutically acceptable salt as alendronate (claims 4, 18, 32-33 and 47-48); the mammal treated (claims 6, 20, 35 and 50); the dosing interval (claims 7, 9, 11, 13, 21, 23, 25, 27, 36, 38, 40, 42, 51, 53, 55 and 57); the dosage amount (claims 8, 10, 12, 14, 22, 24, 26, 28, 37, 39, 41, 43, 52, 54, 56 and 58; and the histamine H2 blocker or proton pump inhibitor (claims 30, 45 and 59).

IV The '342 Patent

The '342 patent, entitled *Dosage Forms Of Risedronate*, issued August 1, 2000, from application S/N 09/303,466 (filed April 30, 1999), which is a continuation of application No. 08/820,430 (filed March 12, 1997). Assigned on its face to The Procter & Gamble Company, Mason, Ohio, the '342 patent lists as inventors Richard John Dansereau, Russell Youker Mosher, Douglas Wayne Axelrod and William Kendall Sietsema, and contains three (3) claims, one (1) of which is independent. The '342 patent is due to expire November 22, 2011.

> 1. A pharmaceutical composition comprising, from 0.15% to 40.00% by weight of a risedronate active ingredient and from 60.00% to 99.75% by weight of excipients comprising: lactose monohydrate, microcrystalline cellulose, crospovidone, and magnesium stearate.

Claims 2-3 depend directly from claim 1. The dependent claims further define: the weight percentage of risedronate and excipients (claims 2-3).

V The '513 Patent

The '513 patent, entitled *Film-Coated Tablet For Improved Upper Gastrointestinal Tract Safety*, issued December 26, 2000, from application S/N 09/095,322 (filed June 10, 1998), which is related to provisional application S/N 60/049,306 (filed June 11, 1997). Assigned on its face to The Procter & Gamble Co., Cincinnati, Ohio, the '513 patent lists as inventors Richard John Dansereau and Petrus Jakobus Bekker, and contains ten (10) claims, of which one (1) is independent. The '513 patent is due to expire June 10, 2018.

> 1. An oral dosage form comprising a safe and effective amount of a bisphosphonate wherein said oral dosage form is oval shaped, about 0.23 to about 0.85 inches in length, about 0.11 to about 0.4 inches in width, and about 0.075 to about 0.3 inches in thickness and said oral dosage form is film coated to facilitate rapid esophageal transit and avoid irritation in the mouth, buccal cavity, pharynx, and esophagus wherein said film coating allows for delivery of said bisphosphonate to the stomach.

Dependent claims 2, 8 and 9 depend from claim 1, while claims 3-4 depend from claim 2. Claims 5-7 depend from the claim immediately preceding them, *i.e.*, claims 4, 5 and 6, respectively. Claim 10 depends from claim 9. The dependent claims further define: the film coating (claims 2-4); the active ingredient (claims 5-6 and 9); the percentage of active (claim 7); and the dosage form (claims 8 and 10).

VI Teva's Bases For Invalidity, Unenforceability Or Non-Infringement

To establish literal infringement, "every limitation set forth in a claim must be found in an accused product, exactly." *Southwall Techs., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1575 (Fed. Cir.), *cert. denied*, 116 S. Ct. 515 (1995). If the independent claims are not infringed there is no infringement of the claims depending from them. *Wahpeton Canvas Co. v. Frontier, Inc.*, 870 F.2d 1546, 1553 (Fed. Cir. 1989). Infringement under the doctrine of equivalents requires that the accused article or composition contain every element of the claims, either literally or as an equivalent. *Unique Concepts v. Brown*, 939 F.2d 1558, 1562 (Fed. Cir. 1991). This doctrine cannot erase "meaningful structural and functional limitations of the claim on which the public is entitled to rely in avoiding infringement." *Pennwalt Corp. v. Durand-Wayland, Inc.* 833 F.2d 931, 935 (Fed. Cir. 1987) (*en banc*), *cert. denied*, 485 U.S. 1009 (1988) (quoting *Perkin-Elmer Corp. v. Westinghouse Elec. Corp.*, 822 F.2d 1528, 1532 (Fed. Cir. 1987).

Prosecution history estoppel limits the doctrine of equivalents. As noted in *Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1460 (Fed. Cir. 1998) (*en banc*), "[p]rosecution history estoppel provides a legal limitation on the application of the doctrine of equivalents by excluding from the range of equivalents subject matter surrendered during prosecution of the application for the patent."

One cannot infringe an invalid claim. *See Richdel, Inc. v. Sunspool Corp.*, 714 F.2d 1573, 1580 (Fed. Cir. 1983) ("The claim being invalid there is nothing to be infringed.").

A. Teva's Tablets Would Not Infringe, Either Literally Or Via Equivalents, Any Claim Of The '342 And '513 Patents, And At Least Claims 1, 5-10, 15, 17-19 And 22 Of The '122 Patent, Claims 3-4, 6-15, 18-19, 21-29, 32-33 And 35-43 Of The '329 Patent, And Claims 3-4, 6-14, 17-18, 20-28, 32-33, 35-43, 47-48 And 50-58 Of The '801 Patent

1. The '342 Patent

Teva's tablets would not literally infringe any claim of the '342 patent because they will not contain either microcrystalline cellulose, or crospovidone

Moreover, the '342 patent formulations are almost identical to those of the prior art. *See e.g.,* U.S. Pats. Nos. 5,358,941 ("the '941 patent"); 5,681,590 ("the '590 patent"); 6,090,410 ("the '410 patent"); and, 6,194,004 ("the '004 patent"). For example, the '941 patent teaches formulations containing bisphosphonates (including risedronate), lactose, microcrystalline cellulose, magnesium stearate, and a disintegrant. Although the preferred disintegrant is croscarmallose sodium, one may use other disintegrants. *See, e.g.,* '941 Pat., claim 1. In addition, while the preferred lactose is anhydrous lactose, one may also use hydrous fast flow lactose, or other forms of lactose. *See id.,* Col. 2, line 4.

As a result, the doctrine of equivalents cannot expand the claims of the '342 patent to cover Teva's tablets without impermissibly covering the prior art. Therefore, Teva's tablets would not infringe the '342 patent, either literally or under the doctrine of equivalents.

2. The ' 513 Patent

Teva tablets would not literally infringe any claim of the '513 patent because they are not oval shaped. During prosecution of the application leading to the '513 patent, the applicants argued that the phrase "generally oval form" in the claims did not render them indefinite. In support, the applicants cited *Tableting Specification Manual* 4th Ed. (1995), and Chapter 7 of *Pharmaceutical Dosage Forms* 2nd Ed., which, *inter alia,* distinguishes between oval and round tablets. The applicants also argued over the rejection of the claims by stating that U.S. Pats. Nos. 5,146,730 and 5,658,589 cited by the examiner did not "teach or suggest oval shaped tablets comprising a bisphosphonate active ingredient that are within Applicants' claimed dimensions and that achieve delivery of the active to the stomach."

As a result of these arguments, the patentee is estopped from attempting to expand the claims under the doctrine of equivalents to cover round tablets, or tablets with dimensions other than those specified in the claims.

Further, the '342 patent is prior art to the '513 patent under 35 U.S.C. § 102(e). The '342 patent describes both round and oval, film-coated tablets containing risedronate. *See* Example I, Col. 14, lines 36, and Example III, Col. 16, lines 1-34. While the '342 patent discloses enteric-coated dosage forms, other non-enteric coated tablet forms of risedronate existed in the prior art. *See e.g.,* the '941 patent. The skilled artisan would have found it obvious to make round or oval, film-coated tablets with non-enteric coatings, with the reasonable expectation that such tablets would effectively deliver bisphosphonates to the stomach and prevent irritation of the esophagus and pharynx. Thus, the '513 patentees cannot use the doctrine of equivalents to expand the claims to cover Teva's tablets without impermissibly covering the prior art.

3. The '122, '329 And '801 Patents

Teva's tablets would not infringe any of at least claims 1, 5-10, 15, 17-19 or 22 of the '122 patent, either literally or via equivalents, since these claims do not cover risedronate or its use.

Likewise, Teva's tablets would not infringe any of at least claims 3-4, 6-15, 18-19, 21-29, 32-33 or 35-43 of the '329 patent, either literally or via equivalents, as these claims do not cover risedronate or its use. For this same reason, Teva's tablets would not infringe any of at least claims 3-4, 6-14, 17-18, 20-28, 32-33, 35-43, 47-48 and 50-58 of the '801 patent, either literally or via equivalents, as these claims do not cover risedronate or its use.

B. Bases For Non-Infringement Of The '329 And '801 Patent Method Of Treatment Claims

1. Teva Would Not Directly Infringe The '329 Or '801 Patent Claims

Teva would not directly infringe the method claims of the '329 or '801 patents under § 271(a), since Teva would not administer its risedronate tablets to a patient.

2. The Manufacture, Sale, Or Offer For Sale Of Teva's 5 And 30 mg Tablets Would Neither Induce Nor Contribute To Infringement Of Any Claim Of The '329 Or '801 Patents

Section § 271(b) provides: "Whoever actively induces infringement of a patent shall be liable as an infringer." Liability for actively inducing infringement under 35 U.S.C. § 271(b) depends upon a finding of direct infringement by others. *See Aro Mfg Co. v. Convertible Top Co.*, 365 U.S. 336, 341 (1960); *Met-Coil Sys. Corp. v. Korners Unlimited, Inc.*, 803 F.2d 684, 687 (Fed. Cir. 1986). "[P]roof of actual intent to cause the acts which constitute the infringement is a necessary prerequisite to finding active inducement." *See Hewlett-Packard Co. v. Bausch & Lomb Inc.*, 909 F.2d 1464, 1469 (Fed. Cir. 1990). Mere knowledge of such infringement does not constitute inducement. *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348 (Fed. Cir. 2003); *Manville Sales Corp. v. Paramount Sys., Inc.*, 917 F.2d 544, 553 (Fed. Cir. 1990).

a. The Use Of Teva's 5 And 30 mg Dosage Strengths Would Not Infringe Any Claim Of The '329 Patent

Teva's 5 and 30 mg tablets used in accordance with Teva's labeling would not induce infringement of the '329 patent claims. Teva's labeling will neither recommend, nor suggest that a patient take 5 or 30 mg tablets, or a combination of 5 and 30 mg tablets on a less-than-daily schedule. Generic drug prescribing information (labeling) which does not suggest a patented method of using the drug cannot, by itself induce infringement of that patented method. Merely supplying a drug that one could use in a patented method cannot induce infringement, particularly when the labeling does not expressly suggest the use of that drug in that method. *See Warner-Lambert Co.*, 316 F.3d 1348.

It is not an infringing act to sell, or offer to sell in the U.S. a composition which can be used in practicing a patented process or method, if the composition is a staple article or commodity of commerce suitable for substantial non-infringing use. 35 U.S.C. § 271(c). Marketing Teva's tablets with Teva's labeling will not render Teva liable for contributory infringement under § 271(c), since Teva's tablets are a staple article or commodity of commerce suitable for a substantial non-infringing use; namely, daily administration. Claims 1-43 of the '329 patent are directed to methods of administering a drug on a less-than daily schedule, *e.g.*, weekly. Teva's 5 and 30 mg tablets are solely for daily administration. As a result, Teva's 5 and 30 mg tablets will not contribute to the infringement of any of the '329 patent claims because there are suitable, substantial non-infringing uses, *i.e.*, daily administration as directed in the proposed labeling.

b. The Use Of Teva's 5 And 30 mg Dosage Strengths Would Not Infringe Any Claim Of The '801 Patent

Similarly, Teva's 5 and 30 mg tablets used in accordance with Teva's labeling would not induce infringement of the '801 patent claims. As mentioned, Teva's labeling will neither recommend, nor suggest that a patient take 5 or 30 mg tablets, or a combination of 5 and 30 mg tablets on a less-than-daily schedule. Labeling that does not suggest a patented method of use cannot by itself induce infringement of a patented method. *See Warner-Lambert Co.*, 316 F.3d 1348. Simply supplying a drug

that one could use in a patented method cannot induce infringement, particularly when the labeling does not expressly suggest the use of that drug in that method.

Nor is it an infringing act to sell, or offer to sell in the U.S. a composition that one can use in practicing a patented process or method, if the composition is a staple article or commodity of commerce suitable for substantial non-infringing use. 35 U.S.C. § 271(c). Teva's tablets, used in accordance with Teva's labeling will not render Teva liable for contributory infringement under § 271(c), since Teva's tablets are a staple article or commodity of commerce suitable for a substantial non-infringing use; namely, daily administration. Teva's 5 and 30 mg tablets are solely for daily administration. As a result, Teva's 5 and 30 mg tablets will not contribute to the infringement of any of the '801 patent claims.

Claims 29-59 of the '801 patent are directed to methods of treating or preventing a condition or disease state by administering a histamine H2 receptor blocker or a proton pump inhibitor ("PPI"), in addition to a unit dose of a bisphosphonate. Teva's labeling will not indicate co-administration of risedronate and a histamine H2 receptor blocker or a PPI. Therefore, use of Teva's tablets in accordance with Teva's labeling would not induce the infringement of any of claims 29-59 of the '801 patent.

Nor would the use of Teva's tablets in accordance with Teva's labeling contribute to the infringement of any of claims 29-59 of the '801 patent. This is because there is a substantial non-infringing use for Teva's 5, and 30 tablets, namely, administration of Teva's tablets without histamine H2 receptor blockers or a PPI.

3. The Manufacture, Sale, Or Offer For Sale Of Teva's 35 mg Tablets Would Neither Induce Nor Contribute To The Infringement Of At Least Claims 10-15, 24-29 and 38-43 Of The '329 Patent Or Claims 9, 11, 13, 23, 25, 27, 38, 40, 42, 53, 55 And 57 Of The '801 Patent

Claims 10-15, 24-29 and 38-43 of the '329 patent are limited to twice-weekly, biweekly or twice-monthly administration. Teva's labeling directs either daily or weekly administration of 35 mg tablets. Labeling that does not suggest a patented method of use cannot by itself induce infringement of a patented method. *See Warner-Lambert Co.*, 316 F.3d 1348. Simply supplying a drug that one could use in a patented method cannot induce infringement, particularly when the labeling does not expressly suggest the use of that drug in that method. Consequently, used in accordance with Teva's labeling instructions Teva's 35 mg tablets would not induce infringement of these claims of the '329 patent.

The use of Teva's 35 mg tablets in accordance with Teva's labeling will not render Teva liable for contributory infringement under § 271(c), since Teva's 35 mg tablets are a staple article or commodity of commerce suitable for a substantial non-infringing use; namely, daily or weekly administration. Teva's 35 mg tablets are not indicated for twice-weekly, biweekly or twice-monthly administration. As a result, Teva's 35 mg tablets would not contribute to the infringement of claims 10-15, 24-29 and 38-43 of the '329 patent.

For similar reasons, claims 9, 11, 13, 23, 25, 27, 38, 40, 42, 53, 55 and 57 of the '801 patent are not infringed. These claims are limited to twice-weekly, biweekly or twice-monthly administration of a bisphosphonate. As mentioned, Teva's labeling will direct either daily or weekly administration of Teva's 35 mg tablets. Administration of Teva's 35 mg tablets in accordance with Teva's labeling would not result in induced infringement of these claims of the '801 patent. Moreover, Teva's 35 mg tablets are a staple article or commodity of commerce suitable for a substantial non-infringing use, *i.e.*, daily or weekly administration. Thus, Teva's 35 mg tablets would not contribute to the infringement of claims 9, 11, 13, 23, 25, 27, 38, 40, 42, 53, 55 and 57 of the '801 patent.

C. At Least Claims 2-3, 11-14 and 20-21 Of The '122 Patent, Claims 1-2, 5, 16-17 and 30-31 Of The '329 Patent, And Claims 1-2, 5, 15-16 and 19 Of The '801 Patent Are Anticipated Under § 102

Section 102(a) provides that a person is entitled to a patent unless " the invention was known or used by others in this country . . . before the invention thereof by the applicant for patent." 35 U.S.C. § 102(a). Section 102(b) entitles a person to a patent unless "the invention was patented or described in a printed publication in this or a foreign country . . . more than one year prior to the date of the application for patent in the United States." 35 U.S.C. § 102(b).

Anticipation under §§ 102(a) & (b) requires that the prior art expressly or inherently disclose the claimed invention. When the disclosure in a reference inevitably leads to a result that result is "inherent", and considered part of the disclosure for anticipation. *See Verdegaal Bros, Inc. v. Union Oil Co.*, 814 F.2d 628, 633 (Fed. Cir.), *cert denied*, 484 U.S. 827 (1987). Moreover, an inevitable result of an express disclosure is an inherent part of the disclosure whether or not anyone at the time recognized that inherent result. *Schering Corp. v. Geneva Pharma., Inc.*, 339 F.3d 1373 (Fed. Cir. 2003).

1. The '122 Patent

Claims 2-3, 11-14 and 20-21 of the '122 patent are anticipated because U.S. Pat. No. 4,761,406 ("the '406 patent"), discloses species falling within subgenera of these claims. "A generic claim cannot be allowed to an applicant if the prior art discloses a species falling within the claimed genus." *In re Gosteli*, 872 F.2d 1008 (Fed. Cir. 1989).

The '406 patent discloses an "invention relate[ed] to a method of treating or preventing osteoporosis, in humans . . . [by administering] . . . a bone resorption inhibiting polyphosphonate". Moreover, this patent teaches, *inter alia*, a method for treating or preventing osteoporosis comprising administration of a bone resorption inhibiting polyphosphonate, and a kit for use in this method of treatment. A specific example of such a polyphosphonate is pyr-EHDP, which is a preferred compound. *See* '406 Pat., Col. 5, lines 50-51.

Risedronate and pyr-EHDP are virtually structurally identical, the difference arising from the point of attachment of the pyridine ring to the linking chain. Pyr-EHDP is attached to the ethane linker via the 2-carbon of the pyridine ring, while risedronate is attached to this linker via the 3-carbon.

Claims 2-3 of the '122 patent are directed to diphosphonic acid compounds, and pyr-EHDP is a species of diphosphonic acid compound within the genus of compounds recited in these claims. Consequently, the '406 patent disclosure of pyr-EHDP anticipates claims 2 and 3 of the '122 patent.

Claims 11-14 of the '122 patent are directed to compositions comprising diphosphonic acid compounds administered with a pharmaceutical carrier. The '406 patent teaches such compositions because it discloses administering diphosphonates in a 1% solution of 0.9% NaCl. The genus of compounds in claims 11-12 of the '122 patent is identical to that of claims 2 and 3, which cover pyr-EDHP. Claim 13 recites a subgenus, which covers pyr-EDHP when R3 is H and the pyridine ring is attached to C_1 at the 2 position. Claim 14 recites a subgenera that names pyr-EHDP as one of the included compounds. Therefore, the '406 patent anticipates composition claims 11-14 since it discloses a pharmaceutical carrier and pyr-EHDP, which falls within the subgenera recited in claims 11-14.

Claims 20-21 of the '122 patent are also anticipated by the '406 patent. These claims merely add the additional limitation of "treating diseases associated with abnormal calcium and phosphate metabolism" to claims 12 and 14. The '406 patent anticipates claims 20-21 because it discloses treating osteoporosis, which the '122 specification sets forth as specifically within the scope of "diseases associated with abnormal calcium and phosphate metabolism."

2. At Least Claims 1-2, 16-17 and 30-31 Of The '329 Patent, And Claims 1-2, 5, 15-16 and 19 Of The '801 Patent Are Anticipated By *Lunar News* (July 1996)

Lunar News (July 1996), comments generally on bisphosphonates, and on alendronate in particular. This publication notes that bisphosphonates are "a major focus for researchers dealing with osteoporosis," and inhibit bone resorption by direct osteoclast action. The reference discusses alendronate, and findings that it increases bone mineral density (BMD), and decreases fracture rates through bone resorption inhibition. Moreover, this reference notes the difficulties with dosing alendronate and suggests weekly administration.

> The difficulties of oral bisphosphonates may favor their episodic (once/week), or cydical (one week each month) administration. Even oral alendronate could be given in a 40 or 80 mg dose once/week to avoid dosing problems and reduce costs.

This statement entirely discloses the methods of claims 1-2, 16-17, 30 and 31 of the '329 patent. Since the narrower claims related to the use of certain bisphosphonates are anticipated by this publication, *i.e.*, claims 2, 17 and 31, the broader, independent claims from which they depend are anticipated as well with respect to the use of the listed bisphosphonates, including risedronate, *i.e.*, claims 1, 16 and 30.

For example, the *Lunar News* discloses oral administration of alendronate to inhibit bone resorption in patients with resorption diseases like osteoporosis. The reference also teaches use of higher unit doses of alendronate on less than a daily basis (*e.g.*, weekly), to avoid dosing problems and reduce costs. A skilled artisan would have understood that the July 1996 *Lunar News* taught the use of "pharmaceutically effective" amounts of the compound, and would have expected such a regime to effectively treat the condition. Thus, this reference anticipates claims 2, 17 and 31 of the '329 patent.

The skilled artisan would have appreciated the inherently disclosed means to prevent osteoporosis through the use of alendronate from this reference. A disclosure of "treating" osteoporosis, such as that found in the *Lunar News*, also discloses "preventing" the same condition.

Similarly, *Lunar News* (July 1996), fully discloses the methods in claims 1-2 and 15-16 of the '801 patent. Since the narrower claims related to certain bisphosphonate use are anticipated, *i.e.*, claims 2 and 16, the broader, independent claims from which they depend, *i.e.*, claims 1 and 15, are necessarily anticipated with respect to the use of the listed bisphosphonates.

As mentioned, this reference discloses oral administration of alendronate to inhibit bone resorption in those with resorption diseases like osteoporosis. It also teaches use of higher unit doses of alendronate on less than a daily basis (*e.g.*, weekly) to avoid dosing problems and reduce costs. A skilled artisan would have understood that this reference taught the use of "pharmaceutically effective" amounts of the compound, and would have expected such a regime to effectively treat the condition. Thus, claims 1-2 and 15-16 of the '801 patent are anticipated.

We note that the district court for the district of Delaware has found that *different* claims of the '329 patent specifically relating to sodium alendronate were not proven to be anticipated or obvious in view of this prior art. None of the claims considered in this section were considered by that court. In addition, it is Teva's opinion that that case was wrongly decided, and has appealed the decision.

3. At Least Claims 1-2, 16-17 And 30-31 Of The '329 Patent, And Claims 1-2 And 15-16 Of The '801 Patent Are Anticipated By *Lunar News* (April 1996)

Lunar News (April 1996), also discusses bisphosphonate use.[1] This reference notes that "all bisphosphonates depress bone turnover, particularly resorption," and that potent bisphosphonates such as alendronate can produce a 50 percent reduction in spinal fractures. The article further discloses the reported sustained responses obtained from intravenous injection of high-dose alendronate, and the lack of evidence of osteomalacia with high oral doses of alendronate (40 mg/day) in Paget's disease.

The *Lunar News* (April 1996), notes the difficulty in patient compliance with the required alendronate dosing regimens, and suggests weekly dosing as a way to improve compliance.

> An intermittent treatment program (for example, once per week, or one week every three months), with higher oral dosing, needs to be tested. A sustained response has been demonstrated to intravenous administration of high-dose alendronate.

The disclosure in this prior art exactly matches many of the claims in the '329 patent. Moreover, based upon this reference, the skilled artisan would have expected the higher dose and less than daily regimen (*e.g.*, weekly dosing) would achieve its intended purpose.

For example, this reference discloses alendronate use to inhibit bone resorption in those with resorption diseases requiring such treatment, *e.g.*, osteoporosis. The reference teaches oral alendronate administration, and the difficulties encountered by patients taking it orally. It also discloses the use of higher unit dosages of alendronate on a less than daily basis, and that a sustained response is demonstrated even with a single alendronate dose. Thus, the skilled artisan would have understood that the April 1996 *Lunar News* taught the use of "pharmaceutically effective" amounts of the compound and would have expected such a regimen to have effectiveness. As such, at least claims 1-2, 16-17, 30 and 31 of the '329 patent are anticipated by the *Lunar News* (April 1996).

Similarly, this reference anticipates at least claims 1-2 and 15-16 of the '801 patent. A skilled artisan would have understood that *Lunar News* (April 1996), taught the use of "pharmaceutically effective" amounts of the compound and would have expected such a regimen to have effectiveness. As such, at least claims 1-2 and 15-16 of the '801 patent are anticipated.

4. At Least Claims 1-2 Of The '329 Patent And Claims 1-2 And 15-16 Of The '801 Patent Are Anticipated By *Reddy*

Reddy, *J. Periodontology*, 66, 211-17 (1995) ["*Reddy*"], discloses oral administration of alendronate and a method for inhibiting increased bone resorption associated with periodontitis progression in a beagle dog model, and amounts of "alendronate" effective in inhibiting bone resorption. As such, it anticipates at least claims 1-2 of the '329 patent. Although *Reddy* does not expressly disclose the use of alendronate for prevention of periodontal disease, it states that the dog model used "may provide a more rigorous challenge for the test of proposed preventative and regenerative periodontal therapy." *Id.* at 212. A skilled artisan would recognize the inherent teaching in *Reddy* for the prevention of periodontal disease. The disclosure for "treating" periodontitis such as in *Reddy*, also discloses "preventing" the same bone resorption disease. At a minimum, the skilled artisan would have found the "prevention" claims obvious in light of *Reddy*.

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[1] The April 1996 *Lunar News* published more than one year before the July 22, 1997, priority date for the '801 patent application, and is prior art under 35 U.S.C. § 102(b).

Reddy also anticipates at least claims 1-2 and 15-16 of the '801 patent. As noted, *Reddy* discloses: treating periodontal disease in a beagle dog model; oral, once-a-week administration of alendronate to treat periodontal disease in beagle dogs in an amount effective in reducing bone loss. Thus, claims 1-2 and 15-16 of the '801 patent are anticipated by this reference as well.

5. At Least Claims 1-2 And 5 Of The '329 Patent And Claims 1-2, 5, 15-16 And 19 Of The '801 Patent Are Anticipated By PCT Application WO95/00288

PCT application WO95/00288 ["*Goodship*"], describes administration of bisphosphonates to prevent prosthesis loosening and migration. It also discloses that arthroplasty is common treatment for those with osteoporotic fracture. *Goodship* teaches the use of bisphosphonates, including risedronate, for the prevention and treatment of periprosthetic osteolysis following arthroplasty. In addition, *Goodship* discusses oral administration of the compound, and that "the dose mentioned above – either administered as a single dose (which is preferred) or in several partial doses – may be repeated, either once daily, once weekly, once every month, once every three months, once every six months or once a year." *See Goodship* at 7. As such, *Goodship* anticipates at least claims 1-2 and 5 of the '329 patent.

Goodship discloses, *inter alia*: oral administration and once-weekly dosing of risedronate; a method of using pharmaceutically effective amounts of risedronate in a range of dosages; use of risedronate to inhibit resorption occurring in bone around prostheses; and, use of bisphosphonates to inhibit excessive bone resorption in a variety of diseases, such as Paget's disease, osteoporosis and hypercalcemia. The skilled artisan would recognize that the treatment and prevention of conditions and diseases is an inherent aspect of the *Goodship* disclosure. Thus, at least claims 1-2, 5, 15-16 and 19 of the '801 patent are anticipated by *Goodship*.

D. Bases Of Invalidity Under § 103(a)

While a patent enjoys a statutory presumption of validity, *see* 35 U.S.C. § 282, a claim is invalid if obvious in view of the prior art. A party can overcome this presumption by clear and convincing evidence that in view of the prior art, a person of "ordinary skill in the art" at the time of making the claimed invention would have found it obvious. *Graham v. John Deere Co.*, 383 U.S. 1 (1966), sets forth the criteria to determine the obviousness or unobviousness of a claimed invention – criteria which include factual findings respecting: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) secondary considerations such as a long-felt need for the claimed invention, commercial success of the invention, and failure of others to achieve the invention. *Id.* at 17-18.

One may demonstrate a *prima facie* case of obviousness when chemical compounds are structurally similar with similar utility. *In Re Payne*, 606 F.2d 303, 313 (C.C.P.A. 1979).

1. The '329 And '801 Patents

a. The Level Of Ordinary Skill In The Art

The prior art demonstrates a reasonably high level of skill. One of ordinary skill to whom the '329 and '801 patents are directed would have at least an M.D. or Ph.D. degree and a number of years of experience in bone diseases. Such a person would have familiarity with the scientific literature on the use of bisphosphonates for inhibiting bone resorption and for the treatment and prevention of osteoporosis and other resorption diseases. This person would have easily understood the prior art references and have the capability to draw inferences from them.

b. The Scope And Content Of The Prior Art

Confidential: Teva Pharmaceuticals USA, Inc.'s Detailed Statement Of The Factual And Legal Bases For Its Opinion That U.S. Patents Nos. 5,583,122, 5,994,329, 6,015,801, 6,096,342, And 6,165,513 Are Invalid, Unenforceable Or Not Infringed By The Manufacture, Use Or Sale Of Teva's 5, 30 And 35 Mg Risedronate Sodium Tablets

Before July 1996, the skilled artisan would have known that administration of risedronate on a less than daily basis in animals effectively inhibited bone resorption, and that oral risedronate is well-tolerated with no significant gastrointestinal effects, and might have better oral tolerability than alendronate. For example, the prior art includes, but is not limited to: U.S. Pats. Nos. 5,730,715 ("the '715 patent"), entitled *Method For The Iontophoretic Administration Of Bisphosphonates*, which discloses, *inter alia*, that "[b]isphosphonates have a strong affinity for calcium and are, therefore, strongly bound to bone for extended period (years). Consequently, one could give bisphosphonates in higher than typical daily doses to patients for treatment of osteoporosis and other bone related disorders at intervals greater than a day (*e.g.*, twice weekly, weekly, monthly, bi-monthly, tri-monthly or once every six months)." Col. 2, lines 38-44. Bisphosphonates identified in the disclosure include risedronate. Col. 4, lines 43-47.

U.S. Pat. No. 5,869,471 ("the '471 patent"), entitled *Methods for the Treatment of Arthritis Using Phosphonates and NSAIDS*, discloses that one can orally administer risedronate once-weekly in humans. As stated in the specification, bone loss or alteration of bone turnover can result from or be associated with many types of arthritis. Col. 1, lines 20-21. Bisphosphonates, including risedronate, are used to inhibit bone loss.

Prior art articles include: Tang *et al.*, J. Bone Min. Res. 7(9): 1093-104 (1992) (a study to reverse existing osteoporosis by restoring and maintaining bone in osteopenic female rats, showed, *inter alia*, bone restored from anabolic treatment followed by risedronate twice-weekly is effectively maintained); Jee *et al.*, J. Bone Min. Res. 10(6): 963-70 (1995) (risedronate continued to inhibit bone resorption even after discontinuation of risedronate treatment); Ma *et al.*, J. Bone Min. Res. 10(6): 963-70 (1995) (twice-weekly risedronate is a superior agent for inhibiting bone resorption compared to other such agents (*e.g.*, estradiols or calcitonin), due to the long term retention of risedronate in bone); and, Seedor *et al.*, J. Bone Min. Res. 6, 339-46 (1991) (study of administration of alendronate to evaluate "the effect of using different dosing regimens to deliver the same skeletal load of drug").

A published review article by Francis, entitled *Oral Bisphosphonates in the Treatment of Osteoporosis: A Review*, 56(9) Curr. Ther. Res. 831-51 (1995), noted that "[t]he most common adverse events with oral bisphosphonates are gastrointestinal disturbances." Although alendronate is "well tolerated, and the incidence of gastrointestinal adverse events is comparable to that with placebo" alendronate is associated with potentially higher incidences of gastrointestinal effects. *Id.* at 844-45. In contrast, clinical trials with oral risedronate resulted in "no significant gastrointestinal adverse events."

In March 1996, Merck distributed a "Dear Doctor" letter to physicians, which discussed the incidence of esophageal irritation. According to Merck, alendronate, administered correctly, is well tolerated and caused essentially no adverse gastrointestinal events.

As previously noted, *Goodship* discloses orally administered risedronate on a weekly basis at a dosage that corresponds to that used in treatment of bone diseases, such as osteoporosis and Paget's disease. *Goodship* discloses single-dose administration of risedronate and alendronate, including single doses administered weekly, not merely "partial" doses. Moreover, the claims of the patents in this case contain no limitation directed to gastrointestinal effects, and therefore, it is irrelevant that Goodship contains no discussion of that issue.

The '329 and '801 patents cite an alendronate study by Chesnut *et al.*, for the proposition that gastrointestinal effects of bisphosphonates increase with increasing dose. '329 Pat., Col. 2, lines 44-51. In fact, an opposite conclusion has resulted in some studies. Well-tolerated, higher than 10 mg daily doses of alendronate are amply documented in the prior art. Few, if any significant side effects are reported regarding 40 mg daily doses of alendronate for Paget's disease, which doses became available in September 1995. A 1996 study of Paget's patients given 40 mg daily doses for six months, noted "no evidence of any increase in upper gastrointestinal adverse experiences." Reid *et al.*, American J. Med.

101, 341-48 (October 1996). Similarly, a 1997 study on the treatment of 60 patients with Paget's disease with 40 or 80 mg of alendronate sodium daily concluded that "no apparent relationship" existed between dose and incidence of side effects. Khan *et al.* Bone 20(3); 263-271 (1997).

These studies would have led the skilled artisan to the reasonable belief that a patient would well tolerate a weekly dose of 35 mg risedronate, since the prior art suggests that risedronate is at least as well tolerated as alendronate.

c. Differences Between '329 Patent Claims 1-2, 5, 16-17, 20, 30-31, 34 And 44, Claims 1-2, 5, 15-16 And 19 Of The '801 Patent, And The Prior Art

There are no differences of any patentable significance between the subject matter of claims 1-2, 5, 16-17, 20, 30-31, 34 and 44 of the '329 Patent, and claims 1-2, 5, 15-16 and 19 of the '801 patent and the teachings and/or suggestions of the prior art. Sufficient motivation to combine these references exists because they relate to bone resorption conditions and how to prevent such conditions using bisphosphonates.

The '329 and '801 patents assert that "administration of a bisphosphonate at a high relative dosage at a low relative dosing frequency causes *less* adverse gastrointestinal effects, particularly esophageal effects, compared to the administration of a low relative dosage at a high relative dosing frequency." *See* '329 Pat., Col. 3, line 64-Col. 4, line 2 (emphasis added); *see also* '801 Pat., Col. 3, line 65-Col. 4, line 3. This is supported neither by the patent disclosure, nor in fact.

The only data in these patents on risedronate use are those for Group 7 of Example 1. The patents state that the experiments show that risedronate administered at low dosages on consecutive days can cause esophageal irritation. However, the patents contain no data on the less-than-daily administration of risedronate. Additionally, this assertion is not supported by the literature based on actual clinical practice, which demonstrates that risedronate is well-tolerated and does not lead to significant adverse gastrointestinal effects.

Based upon the prior art, the skilled artisan would have found it obvious that one could orally administer risedronate sodium at higher doses on a weekly basis, and that this would effectively and safely inhibit bone resorption. Because a patient would tolerate such doses well, the skill artisan would have the motivation to combine the cited references and administer higher doses of risedronate on a weekly basis. Thus, one of ordinary skill in the art would have found claims 1-2, 5, 16-17, 20, 30-31 and 34 of the '329 patent obvious.

Claim 44 of the '329 patent is directed to a "kit" for oral administration of bisphosphonates according to a dosing scheduled of once-weekly, twice-weekly, biweekly and twice-monthly. Use of a "kit" as a vehicle for storing or organizing tablets adds nothing patentable to the concept of administering risedronate sodium on a weekly basis. The use of "kits" for packaging of pharmaceutical dosage forms existed long before 1996. Many pharmaceuticals used "blister packs," as is shown by the following illustrative products on sale in the U.S. shown in the 1995 *Physician's Desk Reference*. Ergamisol® (levamisole HCl); Rheumatrex® (methotrexate); Medrol® (methylprednisolone); and Zithromax® (azithromycin).

In view of the widespread use of such packaging, one of ordinary skill in the art would have found it obvious to package risedronate sodium tablets intended for use in a less-than-daily regimen into a blister pack, or blister pack including a memory.

Similarly, one of ordinary skill in the art would have found it obvious to orally administer risedronate sodium at higher doses on a weekly basis, and that such administration would effectively and

safely inhibit bone resorption. In light of the known inconvenience of daily dosing, a person would have been motivated to combine the references cited above and administer higher doses of risedronate on a weekly basis. As a consequence, one of ordinary skill in the art would have found claims 1-2, 5, 15-16 and 19 of the '801 patent obvious.

We note that the district court for the district of Delaware has found that *different* claims of the '329 patent specifically relating to sodium alendronate were not proven to be anticipated or obvious in view of this prior art. None of the claims considered in this section were considered by that court. In addition, it is Teva's opinion that that case was wrongly decided, and has appealed the decision.

d. Secondary Considerations

When present a court must consider any objective indicia of nonobviousness, which may often constitute the most probative evidence in the record. *Pentec, Inc. v. Graphic Controls Corp.*, 776 F.2d 309, 315 (Fed. Cir. 1985). A nexus is required between the merits of the claimed invention and any evidence of secondary consideration. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1539 (Fed. Cir. 1983). The objective indicia or "secondary considerations" of nonobviousness, however, do not control the analysis when there is an otherwise strong case of obviousness, such as one based upon art not considered by the Patent Office during prosecution. *Newell Cos., Inc. v. Kenny Mfg. Co.*, 864 F.2d 757, 768-69 (Fed. Cir. 1988).

Common secondary considerations are: (1) commercial success; (2) solution of a longstanding problem (long-felt need); (3) failure of others; (4) widespread recognition; (5) copying; and (6) disbelief by experts that the invention would work for its intended purpose. *Stratoflex, Inc.*, 713 F.2d at 1538.

The prosecution history does not show that the '324 and '801 patentees relied on any meaningful secondary considerations to obtain allowance of the patent. Nor is Teva aware of any such evidence arising from the merits of the subject matter of any of the '324 and '801 patent claims. No substantial evidence demonstrates that the claimed "invention" solved longstanding problems or addressed long-felt needs. There is no apparent widespread recognition in the industry of the merits of the claimed "invention." Nor is there any apparent disbelief by experts that the claimed "invention" would work for its intended purpose.

Even assuming, *arguendo*, that a weekly dosage form of risedronate is successful commercially, there is no evidence that such success is related to any aspect of the "invention" in the '329 or '801 patents. Thus, Teva is unaware of any evidence that overcomes the strong case of obviousness regarding the '329 and '801 patent claims. As a consequence, no secondary considerations overcome the otherwise strong case of obviousness that exists in connection with the '324 and '801 patent claims.

2. The '122 Patent

a. The Level Of Ordinary Skill In The Art

For the '122 patent, the prior art also demonstrates a reasonably high level of skill. One of ordinary skill would have substantial training in therapy for osteoporosis, medicinal chemistry and in formulating pharmaceutical products. Such a person would have easily understood the prior art references and have the capability to draw inferences from them.

b. The Scope And Content Of The Prior Art

Relevant prior art includes, but is not limited to: the background section of the '122 application, which acknowledges that the prior art includes polyphosphonic acids and pharmaceutically-acceptable salts as proposed treatments for abnormal calcium and phosphate metabolism. Examples of compounds

used for calcium disorder treatment are ethane-1-hydroxy-1,1-diphosphonic acid (EDHP), propane-3-amino-1-hydroxy-1,1-diphosphonic acid (APD), and dichloromethane diphosphonic acid (Cl_2 MDP). In addition, the prior art also includes, but is not limited to: U.S. Pats. Nos. 4,416,877 ("the '877 Patent"); and, 3,400,150 ("the '150 patent"). Prior art to the CIP includes, but is not limited to the '406 patent.

The '406 patent, assigned on its face to The Procter & Gamble Company, discloses, *inter alia*, a method for treating or preventing osteoporosis comprising administration of a bone resorption inhibiting polyphosphonate. It further discloses a kit for use in implementing this method of treatment. Specific examples of bone resorption inhibiting polyphosphonates include pyr-EHDP, which is cited as a preferred compound.

Risedronate and pyr-EHDP are nearly identical structures, the difference between the two compounds pertaining to the point of attachment of the pyridine ring to the linking chain. Pyr-EHDP is attached to the ethane linker via the 2-carbon position of the pyridine ring, while risedronate is attached to the ethane linker via the 3-carbon position.

The '406 patent further discloses that polyphosphonates are evaluated for *in vivo* bone resorption inhibition potency by an animal model system known as the thyroparathyrolidectomized (TPTX) rat model. Polyphosphonates are also evaluated for *in vivo* bone resorption inhibition and mineralization inhibition in an animal model system known in the field of bone metabolism as the Schenk Model.

Moreover, the '406 patent discloses that pyr-EHDP has a much lower effective dose than other compounds in the TPIX rat model and that "bone loss can be inhibited and bone mass can be increased" using pyr-EHDP, and other compounds disclosed in the '406 patent. *See Id.*, col . 13, lines 1-9.

The '877 patent, assigned on its face to Symphar S.A., discloses, *inter alia*, that the diphosphonates of the invention possess antiatherogenic activity, the ability to alter lipoprotein profiles in favor of high density lipoproteins and to directly clear cholesterol from various tissues. Among the compounds disclosed is hydroxy (p-chlorophenyl) methylenediphosphonic acid, as the monosodium salt ("the '877 compound"), which reportedly lowers calcium 20% in hypercalcemic rats. This compound differs from risedronate by substituting a (p-chlorophenyl) methyl group for the ethyl pyridine of risedronate.

The '150 patent, assigned on its face to The Procter & Gamble Company, discloses, *inter alia*, the synthesis of ethane-2-phenyl-1-hydroxy-1,1,diphosphonic acid ("the '150 compound"), and related compounds. Compounds prepared by the process are reportedly valuable sequestering compounds and complex formers for polyvalent metal ions, which the skilled artisan would understand to include calcium. The '150 compound differs from risedronate merely by the substitution of a phenyl group for the pyridine group of risedronate.

c. Differences Between Claims 2-4, 11-14, 16, 20-21 And 23 Of The '122 Patent And The Prior Art

There are no differences of any patentable significance between the subject matter of claims 4, 16 and 23 of the '122 patent. As noted, the '406 patent discloses, *inter alia*, pyr-EHDP, compositions comprising pyr-EHDP, and the use of pyr-EHDP to treat osteoporosis. The pyr-EHDP compound is nearly identical to risedronate. Given the disclosure that pyr-EHDP is more effective than other compounds tested in the TPTX model, one skilled in the art would have motivation to make risedronate with the reasonable expectation that it would have similar properties to pyr-EHDP due to their similar structure. Thus, claims 4, 16, and 23 of the '122 patent, which cover the chemical species of risedronate, are obvious in view of the '406 patent.

In addition, the '122 patent claims to risedronate and subgenera are also obvious over the '150 and '877 patents in view of the state of the art at the time of the invention. The '150 compound and the '877 compound both disclose polyphosphonic acids that contain phenyl rings. As explained, these compounds are both structurally similar to risedronate, differing from it and its larger genus by the substitution of a carbon atom for the nitrogen atom of risedronate's pyridine ring.

Moreover, the skilled artisan would have known of the '150 and '877 compounds, pyr-EHDP, and their similar utility to risedronate. One of ordinary skill in the art would have known that the '150 compound and pyr-EHDP form complexes with polyvalent metal ions such as calcium. In addition, the '877 compound had shown an ability to lower serum calcium in hypercalcemic rats. The prior art also disclosed that one could treat abnormal calcium and phosphate metabolism with polyphosphanates such as pyr-EHDP.

Therefore, the skilled artisan would have found it obvious to substitute a nitrogen atom for a carbon atom in the phenyl ring of the '150 and '877 compounds, with the expectation that the resulting pyridine compound would have similar properties in lowering serum calcium (*i.e.* some resorption). This is because one skilled in the art would have the expectation that compounds similar in structure would have similar properties.

Consequently, claims 4, 16, and 23 of the '122 patent, directed to the chemical risedronate, are obvious in view of the '150 and '877 compounds. Moreover, the '150 and '877 compounds also render claims 2-3, 11-14 and 20-21 of the '122 patent obvious, because these claims, broader in scope than claims 4, 16, and 23, nonetheless cover the species risedronate.

d. Secondary Considerations of Obviousness

Teva is not aware of any evidence of secondary considerations which negate the otherwise strong case of obviousness that exists in regard to the '122 patent. There is no solution of any longstanding problem, failure of others to achieve the result, widespread recognition, copying or disbelief by experts that the invention would work. The prosecution history does not show that the applicants relied upon any meaningful secondary considerations to obtain allowance of the '122 patent claims, nor is Teva aware of any such evidence.

Assuming, *arguendo*, that risedronate is commercially successful, this commercial success arose, at least in large part from the aggressive advertising of risedronate as a well-tolerated oral bisphosphonate, rather than through any invention claimed in the '122 patent. Thus, no evidence of secondary consideration overcomes the clear and convincing obviousness of the claimed invention.

e. Patentability Based Upon "Unexpected Advantages"

The unexpected advantages that allowed the applicants to distinguish their invention from the disclosure of U.S. Pat. No. 4,687,767 ("the '767 patent"), do not render the '122 patent non-obvious in view of the cited prior art.

During an interference with the '767 patentees, the '122 patent applicants argued that risedronate, and other compounds having linking chains with zero or one carbon, are patentably distinct from compounds having two or more carbons in the linking chain because the former compounds are surprisingly more effective than the latter. The applicants suggested that compounds having two or more carbons in the linking chain are not active even at the highest dose tested.

However, the applicants' argument does not distinguish risedronate from the compounds of pyr-EHDP, and the '150 and '877 compounds because these compounds have the same number of carbons in

the linking chain as the genus that includes risedronate. Moreover, unlike compounds with two carbons in the linking chain, which the applicants stated had no activity, the compounds of the '406 patent and the '877 patent lowered serum calcium.

E. Double Patenting

Claims 4, 16 and 23 of the '122 patent are also invalid for obviousness-type double patenting in view of the subject matter claimed by the '406 patent. Both the '122 and '406 patents are assigned to The Procter & Gamble Company. Thus, the '122 and '406 patents satisfy the threshold issue of common relationship of inventorship and/or ownership.

In addition, the '122 and '406 patents arise from separately prosecuted applications. The PTO did not impose a restriction requirement identifying claims of the '122 patent as patentably distinct from those of the '406 patent. Consequently, 35 U.S.C. § 121 does not preclude the use of the '406 patent to establish obviousness-type double patenting of the '122 patent.

1. Obviousness-Type Double Patenting

Generally, the appropriate test of obviousness-type double patenting is the "one way" test, where later issued subject matter is obvious in view of the earlier issued subject matter. *In re Berg*, 140 F.3d 1428, 1432 (Fed. Cir. 1998). "Under special circumstances" the Federal Circuit has made an "exception" to this general rule and applied a two-way test, requiring in addition that the earlier issued claims are also obvious in view of the later issued claims. *Id.* "The two way exception can only apply when the applicant could not avoid separate filings, and even then, only if the PTO controlled the rates of prosecution to cause the later filed species claims to issue before the claims for a genus in an earlier application." *Id.* at 1435.

For those claims of the '122 patent not entitled to the priority of the parent application, and that issued second from a second-filed application, the "one-way" test is appropriate. For those claims of the '122 patent that are entitled to priority of the parent application (*i.e.*, earlier filed, but later issued), the one way test is also appropriate since the PTO is not solely responsible for the delay causing the second filed application to issue prior to the first. To the extent any of the '122 patent claims are entitled to an earlier filing date than the '406 patent, the patentee bears at least partial responsible for delaying the issuance of those claims, since it provoked an interference with the '767 patent. *See Pierce v. Allen B. DuMont Labs., Inc.*, 131 USPQ 340, 345 (3d Cir. 1961) (delay caused by provoking interference charged to applicant).

Thus, the one-way test is appropriate to determine whether any of the claims of the '122 patent are invalid for obviousness-type double patenting.

a. Claims 2-4, 11-12, 14, 16, 20-21 And 23 Of The '122 Patent Are Obvious In View Of The '406 Patent

Claim 15 of the '406 patent recites a method of treating osteoporosis comprising administrating a polyphosphonate selected from a group which includes pyr-EHDP. As discussed above, pyr-EHDP and risedronate are structurally similar, differing only by the point of attachment of a pyridine group. Claims 2-4 of the '122 patent claim, *inter alia*, risedronate or genuses comprising risedronate, and are obvious in view of claim 15 of the '406 patent, which recites pyr-EHDP. One of ordinary skill in the art would have had the motivation to make the compound risedronate and a composition containing it for use in treating

osteoporosis with the expectation that it would have similar properties as pyr-EHDP in the treatment of osteoporosis.[2]

Claims 11-12, 14, and 16 of the '122 patent claim pharmaceutical compositions containing, *inter alia*, risedronate and a pharmaceutically acceptable carrier. The skilled artisan would have found it obvious to use any drug, including risedronate, with a pharmaceutically acceptable carrier.

Claims 20-21 and 23 of the '122 patent claim methods of treating diseases associated with abnormal calcium and phosphate metabolism by administering pharmaceutical compositions containing, *inter alia*, risedronate. Claim 15 of the '406 patent claims a method of treating osteoporosis by administering pyr-EHDP. Osteoporosis is known as a disease associated with abnormal calcium and phosphate metabolism. One of ordinary skill in the art would have found it obvious to use risedronate to treat osteoporosis, and therefore, method claims 20-21 and 23 of the '122 patent are obvious over claim 15 of the '406 patent. Consequently, all these claims of the '122 patent covering risedronate are invalid for double patenting.

VII Conclusion

For the reasons stated above, all claims of U.S. Pats. Nos. 5,583,122, 5,994,329, 6,015,801, 6,096,342, and 6,165,513 are invalid, unenforceable or not infringed, either literally or under the doctrine of equivalents, by the manufacture, use of sale of Teva's 5, 30 and 35 mg risedronate sodium tablets. Teva reserves the right to develop additional grounds, reasons and authorities that any or all of the claims of these U.S. Patents are invalid, unenforceable, or not infringed.

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[2] The applicants argued during prosecution that osteoporosis is a disease of abnormal calcium metabolism. Thus, the applicants are now estopped from asserting that the method for treating osteoporosis in the '406 patent is different than method claim 22 of the '122 patent.

ABBREVIATED NEW DRUG APPLICATION 77-132
OFFER OF CONFIDENTIAL ACCESS
PURSUANT TO 21 U.S.C. § 355(j)(5)(C)(i)(III)

WHEREAS Teva Pharmaceuticals USA, Inc. ("Teva USA") has provided notice to Procter & Gamble Pharmaceuticals, The Procter & Gamble Company, and Merck & Co.,. Inc. (hereinafter "Recipients") that Teva USA submitted to the U.S. Food and Drug Administration ("FDA") Abbreviated New Drug Application 77-132 for Risedronate Sodium Tablets, 5 mg, 30 mg and 35 mg, (referred to hereinafter in whole or in part as the "ANDA") containing a Paragraph IV certification with respect to U.S. Patents 5,583,122, 5,994,329, 6,015,801, 6,096,342 and 6,165,513 (the "Listed Patents") which are listed in the FDA Publication, "Approved Drug Products with Therapeutic Equivalence Evaluations"; and

WHEREAS this document constitutes Teva USA's Offer of Confidential Access to that ANDA pursuant to 21 U.S.C. § 355(j)(5)(C)(i)(III) which provides:

> The document providing the offer of confidential access shall contain such restrictions as to persons entitled to access, and on the use and disposition of any information accessed, as would apply had a protective order been entered for the purpose of protecting trade secrets and other confidential business information. A request for access to an application under an offer of confidential access shall be considered acceptance of the offer of confidential access with the restrictions as to persons entitled to access, and on the use and disposition of any information accessed, contained in the offer of confidential access, and those restrictions and other terms of the offer of confidential access shall be considered terms of an enforceable contract. Any person provided an offer of confidential access shall review the application for the sole and limited purpose of evaluating possible infringement of the patent that is the subject of the certification under paragraph (2)(A)(vii)(IV) and for no other purpose, and may not disclose information of no relevance to any issue of patent infringement to any person other than a person provided an offer of confidential access. Further, the application may be redacted by the applicant to remove any information of no relevance to any issue of patent infringement;
>
> and

WHEREAS Teva USA desires to offer to provide Recipients confidential access to the ANDA subject to restrictions as to persons entitled access to, and on the use and disposition of, the ANDA; and

WHEREAS this document accompanies Teva USA's Notice and Detailed Statement under 21 U.S.C. § 355(j)(2)(B) with respect to the Listed Patents;

NOW, THEREFORE:

1. Pursuant to 21 U.S.C. § 355(j)(5)(C)(i)(III), and subject to the restrictions contained in Section 2 below, Teva USA hereby provides Recipients this Offer of Confidential Access ("Offer") for the sole purpose of determining whether to bring an action referred to in 21 U.S.C. § 355(j)(5)(B)(iii) with respect to the Listed Patents.

2. This Offer is subject to the following restrictions as to persons entitled to access and the use and disposition of any information accessed:

A. **Persons Entitled to Access:** Persons entitled to access ("Authorized Evaluators") under this Offer of Confidential Access are restricted to (i) outside counsel engaged or employed by Recipients to represent them and the staff of such outside counsel, including paralegal, secretarial and clerical personnel who are engaged in assisting such counsel, provided that such outside counsel has been identified to Teva USA in writing, (ii) no more than 2 in-house counsel and the staff of such in-house counsel, including paralegal, secretarial and clerical personnel who are engaged in assisting such counsel, and (iii) independent consultants and experts assisting in the evaluation of possible infringement of the Listed Patents and any employees and assistants under the control of such consultant or expert.

B. **Materials Accessible by Authorized Evaluators:** A copy of the ANDA, redacted to remove information of no relevance to any issue of patent infringement, will be provided for use by Authorized Evaluators.

C. **Use of the ANDA and Information in the ANDA:**

(1) The ANDA and all information contained therein or derived therefrom may be used for the sole and limited purpose of evaluating possible infringement of the Listed Patents and for no other purpose.

(2) Authorized Evaluators shall not disclose any information contained in or derived from the ANDA or any notes, analyses, studies or other documents to the extent that they reflect any information in the ANDA, to any person other than person entitled to access under subsection A.

(3) Notwithstanding the provisions of subsections 2(C)(1) and 2(C)(2) above, Authorized Evaluators shall be permitted to advise Recipients whether or not to bring suit alleging infringement of the Listed Patents; provided, however, that the information in the ANDA is not thereby disclosed.

D. **Disposition of the Information in the ANDA:**

(1) Recipients agree that if they do not file suit against Teva USA alleging infringement of the Listed Patents within 45 days of receipt of the Notice and Detailed Statement (the "45-day period") which this offer accompanies, Recipients shall cause Authorized Evaluators, within 30 days after the expiration of the 45-day period, to destroy or return to Teva the portions of the ANDA provided and all notes, analyses, studies or other documents to the extent that they contain information in the ANDA, and Recipients shall notify Teva that this has been done.

(2) Recipients agree that if any Recipient files suit against Teva USA alleging infringement of the Listed Patents within the 45-day period:

(a) While the litigation is pending, the portions of the ANDA provided and all notes, analyses, studies or other documents to the

extent that they contain information in the ANDA, shall be treated as information under the highest level of confidentiality under any protective order entered in the action brought against Teva USA. Until such a protective order is entered, subsection 2(C)(2) above continues to apply.

(b) Recipients shall cause Authorized Evaluators to destroy or return to Teva the portions of the ANDA provided and all notes, analyses, studies or other documents prepared to the extent that they contain information in the ANDA, within thirty (30) days after the final determination of the action brought against Teva USA.

(3) Notwithstanding the provisions of subsections 2(D)(1) and 2(D)(2) above, each outside law firm authorized to have access pursuant to subsection 2(A)(i) shall be permitted to retain one copy of the portions of the ANDA provided and each note, analysis, study or other document to the extent that they contain information in the ANDA.

E. **Accidental Disclosure**: Should information contained in the ANDA be disclosed, inadvertently or otherwise, Recipients shall, at their earliest opportunity, by and through Authorized Evaluators, contact Teva USA and identify:

(1) what has been disclosed;

(2) the individuals to whom such information has been disclosed; and

(3) steps taken by Recipients and Authorized Evaluators to ensure the information in the ANDA is not further disseminated.

3. Recipients acknowledge that violation of any provision of this Offer will cause irreparable injury to Teva USA, and that an adequate legal remedy does not exist. Teva USA, therefore, shall have the right, in addition to any other remedies available at law or in equity, to obtain from a court of competent jurisdiction an injunction to prohibit Recipients from violating the terms of this Offer. Recipients agree that in such an action Teva USA is entitled to recover any and all damages, costs and expenses, including, but not limited to, all reasonable attorneys' fees, professional fees and court costs.

4. Should any provision set forth in this Offer be found by a court of competent jurisdiction to be illegal, unconstitutional or unenforceable, the remaining provisions shall continue in full force and effect.

5. Nothing contained herein shall be construed as a grant of any license or other right to use the information in the ANDA except for the purpose expressly stated herein.

6. When accepted by Recipients, this document shall constitute the entire agreement of the parties with respect to the subject matter herein and may not be amended or modified except in writing executed by all of the parties.

7. A Recipient may request access to the ANDA by executing one copy of this Offer where indicated and returning the executed copy to Marc A. Goshko. Thereupon, the terms contained in this document shall be considered an enforceable contract between Teva USA and the Recipient.

Teva Pharmaceuticals USA, Inc.
By its authorized agent:

Marc A. Goshko
Senior Director, Legal Affairs

Date: July 2, 2004

Recipient
By its authorized agent:

Signature: _____

Name (Print): _____

Title: _____

Company: _____

Date: _____